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EXAMINER
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FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
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1637

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b>		<b>Applicant(s)</b>	
	10/033,396		BOTSTEIN ET AL.	
	<b>Examiner</b>		<b>Art Unit</b>	
	Jeffrey Fredman		1637	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 23 October 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 22-26 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 22-26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                                   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>10/23/06</u> .  | 6) <input type="checkbox"/> Other: _____                                    |

## DETAILED ACTION

### *Claim Rejections - 35 USC § 101*

1. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 22-26 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of antibodies which bind to a protein termed Pro-539 (SEQ ID NO: 7) or portions thereof, in the specification, where the protein has the amino acid sequence of SEQ ID NO: 7.

#### **Credible Utility**

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the antibody or of the Pro-539 protein to which it binds. The cited utilities in the specification include overexpression in cancer. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the PRO 539 polypeptide or antibody. A review of the specification and of the prior art finds no well established utilities for unknown proteins and antibodies whose activity, whose enzymatic or other biochemical function and whose cellular roles are entirely unknown and undisclosed in the specification.

The next inquiry is whether there are substantial or specific utilities for the antibody to PRO 539 protein which are identified in either the specification or in the prior art.

**Substantial utility**

*No assertion of utility for protein in specification*

The specification is entirely silent with regard to any utility for the PRO539 protein. Further, there is no well established utility for the PRO 539 protein. While Applicant asserts that the PRO 539 protein shares the utility asserted for the PRO 539 nucleic acid as a diagnostic, that assertion is not supported by specific evidence of utility for PRO539 itself as being overexpressed in any cancer cell. The utility assertion for the PRO539 protein is based on a presumed generic relationship between mRNA expression and protein expression that is argued to exist generically. The weight of prior art which analyzes large scale sets of proteins does not support this utility, as discussed next.

**Protein and DNA Microarray data shows no necessary correlation between mRNA overexpression and protein expression**

Seven out of eight microarray papers show discordant protein and mRNA expression data

Seven recent papers provide much stronger evidentiary showings, showing that it is more likely than not that mRNA expression is not correlated with protein expression, while only the Orntoft paper shows a counter example. Czupalla et al (Proteomics

(2005) 5:3868-3875) notes "Comparison of the results for differential expression obtained by the two techniques essentially reveals two groups of genes. The first group comprises 47 genes for which differences in mRNA expression and in abundance of the corresponding proteins spots on 2-D gels were consistently detected (see page 3873, column 2)." After discussing genes, Czupalla continues "In contrast, a second group of 70 gene products comprises those for which we did not observe any changes in mRNA expression although we could clearly detect either increased or decreased protein expression by 2-DE (see page 3874, column 1)." The data of Czupalla, which addresses 117 genes, shows that it is more likely than not in this data set that there is no correlation between mRNA expression and protein expression. This supports the conclusion that mRNA expression cannot be relied upon for enablement and utility of the protein since no necessary correlation exists.

Kwong et al (Genomics (2005) 26:142-158), drawn to colorectal cancer, a disease similar to the one analyzed by Appellant, has even stronger conclusions. Kwong notes that 47 genes had valid protein and mRNA data in the 10 samples and were selected for correlation analysis. Kwong states regarding these samples that "Only 12 of the 47 genes exhibited correlated expression at a significance level less than 0.05. Surprisingly, 13 genes had a negative correlation between mRNA and protein levels. The correlation between protein and mRNA was also compared on a sample-by-sample basis. Of the 53 samples for which data was available, mRNA and protein levels were found to be correlated at a significance level of 0.05 in only 14 samples, while 14 mRNA and proteins were negatively correlated (see page 151,

column 2 to page 152, column 1). Following Kwong, it is clear that it is not more likely than not that protein and mRNA expression are correlated. In fact, Kwong supports the conclusion that it is more likely than not that there is no correlation.

Chen et al (Mol. Cellular Proteomics (2002) 304-313 notes "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein. (see page 311, column 1)" Chen continues a little later "The majority of protein isoforms, however, did not correlate with mRNA levels and thus their expression is regulated by other mechanisms. We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression values (see page 311, column 1)." Chen does refer to Celis (ref. 19 of Chen) who cites Orntoft et al who shows 39 out of 40 proteins correlated in expression between the mRNA and protein levels.

Conrad et al (Mol. Cell Proteomics (2005) 4(9) :1284-1296) performed an analysis on 2501 proteins of which data regarding the abundance of 1900 proteins was aligned with nucleic acid microarray data(see page 1290, column 1). Conrad found that in this very large data set "There is little correlation between RNA and protein abundance identified and predicted by cICAT (see page 1290, column 2)."

Ginestier et al (Am. J. Pathol. (2002) 161:1223-1233) teaches at table 4 that only five out of 15 genes showed concordance. Ginestier notes "For a category of molecules we found important differences between RNA and protein expression levels (see page 1230, column 2)."

Anderson et al (Electrophoresis (1997) 18:533-537) shows that for 19 proteins that were compared between 2D gel electrophoresis and mRNA analysis "the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0) (see page 536, column 1)." In fact, the correlation is slightly closer to showing that there is no correlation whatsoever between protein and mRNA data. This is consistent with the showing of Washburn (Proc. Natl. Acad. Sci. (2003) 100 (6):3107-3112, who analyzed a comparison of 678 loci and found a correlation of 0.45 (see page 3109, column 1), which also shows a correlation that is closer to the absence of correlation than to a positive correlation.

Combining the data from Czupalla, Kwong, Orntoft, Chen and Ginestier, they analyzed 384 genes in total. There was a correlation between the RNA and protein levels for 131 of these genes (with 39 of them being the highly correlated Orntoft paper). This results in a final correlation of 34%, which means that it is more likely than not that there is no correlation between RNA and protein levels.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

*Abundant art supports the absence of a necessary relationship between mRNA and protein*

Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification



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and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

### *Statistical Significance*

The overexpression data does not provide a substantial utility for several reasons. First, there is no showing that the overexpression was statistically significant and correlated with any diagnostic utility. The absence of such a diagnostic utility is particularly striking since there is no evidence that the overexpression effect was statistically significant. While the specification states "Only values that were above this cutoff ratio were determined to be significant" in paragraph 0930, there is no evidence to suggest that this overexpression is statistically significant.

Further, there is no evidence that the overexpression was reproducible. From the data presented in the specification, a single prostate tumor sample from a single patient may have been used. Such a result from a single patient would not support any utility because even if the nucleic acid was overexpressed in the one patient, there would be no expectation that the result would appear in even one other patient, so there is no evidence of record that the overexpression shown has any utility as a diagnostic or for any other purpose. Also, there is no evidence that the overexpression in the

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prostate tumor was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture.

Further, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. The current gene, Pro539, is such a gene. Given the absence of any evidence regarding sample size and the absence of any direct association with

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Pro539 and prostate tumors, this gene represents noise. The prior art suggests that such genes should not be placed on the array. Therefore, genes such as Pro539, lack substantial utility as useful on gene expression arrays.

*Absence of tissue matched controls*

It is important to note that the gene encoding PRO539 was not found to be amplified in twenty-two other listed tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 115). Therefore, the overexpression data itself is questionable, since blood and lung may naturally express PRO539 at different levels. The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy. Given these details, one skilled in the art would not conclude that the gene encoding PRO539 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a small amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Gokman-Polar.).

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was

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found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this case is also similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-539 antibodies and proteins. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

**Specific Utility**

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for the antibody to the PRO-539 protein of SEQ ID NO: 7. The antibody to the protein, as distinguished from the nucleic acid, has not been associated with any disease, any condition, or any other specific feature. There is no association of the antibody or protein with cancer or with any other disease. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, the overexpression of the nucleic acid gives no specific utility because it is entirely unrelated to uses of the protein or antibody. A protein or antibody cannot be used to detect changes in its cognate nucleic acid, as shown by the Gokman-Polar and Meric

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papers, where protein levels are not correlative with nucleic acid levels. Therefore, there is no specific utility for this protein until a specific ligand is identified.

Finally, with regard to the utility analysis, the current situation directly tracks Examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function and a receptor with an unknown ligand was characterized as lacking utility.

### ***Claim Rejections - 35 USC § 112 – Scope of Enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims are drawn to an antibody to the PRO-539 protein of SEQ ID NO: 7. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass not only a particular PRO-539 antibody but also include any antibody which binds the polypeptide of SEQ ID NO: 7.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and nucleic acids. It would require significant study to identify the actual function of the PRO-539 protein and nucleic acid, and identifying a use for this protein and resultant antibody would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as shown by homology, may have very different functions (see Rost et al (*J. Mol. Biol.* (2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely

unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

This data further lacks any of the hallmarks of utility or of any enabled use because the overexpression of the nucleic acid is not relevant to the utility of the protein. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the antibody to the protein itself.

So it is entirely unpredictable how one would use this antibody in any context whatsoever.

#### Working Examples

The specification has no working examples that relate to the antibody or protein. The nucleic acid working examples, showing overexpression in certain cancer cell lines, are not relevant for the reasons given above. Specifically, there is no statistical showing that the overexpression of the nucleic acids is even significant in any way. Even if the nucleic acid data is deemed significant, there is no showing that the results from nucleic acids have any correlation with the protein or antibody and the art cited above demonstrates that there is no presumption of such a correlation.

#### Guidance in the Specification.



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The specification provides no specific or substantial uses for the PRO-539 antibody or protein.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

***Response to Declaration***

4. The Scott Declaration under 37 CFR 1.132 filed October 23, 2006 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. 101 as set forth in the last Office action for the following reasons.

The Scott declaration solely represents the generic opinion of Dr. Scott, without any evidence supporting that opinion. The declaration does not specifically address whether PRO539 is coexpressed and there is no data or argument which addresses this specific molecule.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion.

(1) In the instant case, the nature of the fact sought to be established is whether or not increased mRNA levels are predictive of increased polypeptide levels. This is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Dr. Scott does not aver that the differences he sees in hundreds of thousands of genes on a microarray are compared to a "universal control" of unmatched tissue; instead, Dr. Scott is comparing the level of expression of hundreds of thousands of genes of a specific normal tissue sample compared against a specific cancerous tissue sample, so Dr. Scott is at least comparing normal lung tissue with cancerous lung tissue, normal breast tissue with cancerous breast tissue, etc. (essentially apples compared to apples) and not cancerous tissue with an amalgam of control tissues (essentially apples compared to a mixed composition of apples, bananas, and pears, as the Examiner has previously pointed out and already made of record).

As Dr. Scott indicates, the reason for success in the gene chip or microarray industry is because it can give a quick approximation or first step towards further research for hundreds of thousands of gene targets at once. But, once an appropriate target is identified, further research must be performed to see if the gene in question

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has any relevance to the disease process at hand, and whether its change in expression at the nucleic acid level correlates with a change of expression at the protein level. To paraphrase Brenner v. Manson, the microarray analysis is but the beginning of the search, but it is not its successful conclusion.

(2) There is significant evidence which opposes the conclusion of the Scott declaration. As noted in the rejection above, seven recent papers provide much stronger evidentiary showings, with six showing that it is more likely than not that mRNA expression is not correlated with protein expression, while only the Orntoft paper showing a counter example. Czupalla et al (Proteomics (2005) 5:3868-3875) notes "Comparison of the results for differential expression obtained by the two techniques essentially reveals two groups of genes. The first group comprises 47 genes for which differences in mRNA expression and in abundance of the corresponding proteins spots on 2-D gels were consistently detected (see page 3873, column 2)." After discussing genes, Czupalla continues "In contrast, a second group of 70 gene products comprises those for which we did not observe any changes in mRNA expression although we could clearly detect either increased or decreased protein expression by 2-DE (see page 3874, column 1)." The data of Czupalla, which addresses 117 genes, shows that it is more likely than not in this data set that there is no correlation between mRNA expression and protein expression. This supports the conclusion that mRNA expression cannot be relied upon for enablement and utility of the protein since no necessary correlation exists.

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Chen et al (Mol. Cellular Proteomics (2002) 304-313 notes "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein. (see page 311, column 1)" Chen continues a little later "The majority of protein isoforms, however, did not correlate with mRNA levels and thus their expression is regulated by other mechanisms. We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression values (see page 311, column 1)." Chen does refer to Celis (ref. 19 of Chen) who cites

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Orntoft et al who shows 39 out of 40 proteins correlated in expression between the mRNA and protein levels.

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Anderson et al (Electrophoresis (1997) 18:533-537) shows that for 19 proteins that were compared between 2D gel electrophoresis and mRNA analysis "the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0) (see page 536, column 1)." In fact, the correlation is slightly closer to showing that there is no correlation whatsoever between protein and mRNA data. This is consistent with the showing of Washburn (Proc. Natl. Acad. Sci. (2003) 100 (6):3107-3112, who analyzed a comparison of 678 loci and found a correlation of 0.45 (see page 3109, column 1), which also shows a correlation that is closer to the absence of correlation than to a positive correlation.

Combining the data from Czupalla, Kwong, Orntoft, Chen and Ginestier, they analyzed 384 genes in total. There was a correlation between the RNA and protein levels for 131 of these genes (with 39 of them being the highly correlated Orntoft paper). This results in a final correlation of 34%, which means that it is more likely than not that there is no correlation between RNA and protein levels.

If we further combine the evidence of the Polakis declaration with the data of Czupalla, Kwong, Orntoft, Chen and Ginestier, we end up with 415 genes total, with 159 of them showing RNA/protein correlation. This results in a combined correlation, including the Polakis data, of 38%. This is still in a position where it is more likely than not for any given protein that there is NO correlation between mRNA and protein levels.

(3) Dr. Scott appears to have no direct interest in the case.

(4) There is no factual support for Dr. Scott's position. Dr. Scott does not present any data to rebut the data from Czupalla, Kwon, Orntoft, Chen, Conrad, Anderson or Ginestier.

However, given the very strong data opposing the conclusion of Dr. Polakis, derived from six different papers which represent virtually the totality of the art in this area, with only one paper supporting the position of Dr. Scott, the conclusion is inescapable that there is no necessary correlation between mRNA and protein levels and that in fact, it is not likely for any given protein that such a correlation will exist.

### ***Response to Arguments***

5. Applicant's arguments filed October 23, 2006 have been fully considered but they are not persuasive.

First, the arguments made in the examiner's answer remain applicable.

### **Legal Analysis**

#### **Brenner**

In analyzing utility, the first place to begin is with the decision of the Supreme Court in Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). In Brenner, the Court concluded that “[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.” Id. at 534-35, 148 USPQ at 695.

There is no specific benefit, in currently available form, for the Pro-539 protein or antibody, since there are no specific and substantial utilities for that Pro-539 protein or antibody.

#### **Kirk**

The CCPA first applied Brenner in In re Kirk, 376 F.2d 936, 153 USPQ 48 (CCPA 1967). The invention claimed in Kirk was a set of steroid derivatives said to have valuable biological properties and to be of value “in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice.” Id. at 938, 153 USPQ at 50. The claims had been rejected for lack of utility. In response, the applicants submitted an affidavit which purportedly “show[ed] that one skilled in the art

would be able to determine the biological uses of the claimed compounds by routine tests.” Id. at 939, 153 USPQ at 51.

The court held that “nebulous expressions [like] ‘biological activity’ or ‘biological properties’” did not adequately convey how to use the claimed compounds. Id. at 941, 153 USPQ at 52. Nor did the applicants’ affidavit help their case: “the sum and substance of the affidavit appear[ed] to be that one of ordinary skill in the art would know ‘how to use’ the compounds to find out in the first instance whether the compounds are—or are not—in fact useful or possess useful properties, and to ascertain what those properties are.” Id. at 942, 153 USPQ at 53.

The Kirk court held that an earlier CCPA decision, holding that a chemical compound meets the requirements of § 101 if it is useful to chemists doing research on steroids, had effectively been overruled by Brenner. “There can be no doubt that the insubstantial, superficial nature of vague, general disclosures or arguments of ‘useful in research’ or ‘useful as building blocks of value to the researcher’ was recognized, and clearly rejected, by the Supreme Court” in Brenner. See Kirk, 376 F.2d at 945, 153 USPQ at 55.

The current situation is identical to that in Kirk. The Declarations filed provide evidence that one could determine whether the Pro-539 protein is useful, but do not even show any utility specifically for Pro-539 as discussed above. Further, the discussion cited by Applicant of the various declarations clearly represent language which is “useful in research” but has no current practical use. The speculation by the Declarants that medical practitioners might wish to know if proteins in general are



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overexpressed, without reference to Pro-539 in particular, is precisely the sort of vague argument which lacks any specificity.

Fisher

The Fisher appellant argued that EST expression during anthesis supported a finding of utility since the protein would be expressed. This utility is highly similar to the current utility since both are based upon relative expression of mRNA in a tissue. The Federal Circuit rejected this argument at page 15 of the decision (as posted on the Federal Circuit Web site), noting that no evidence of the claimed expression, which was shared in common with 2000 molecules, was provided in the specification. That is virtually identical to the current case, where Appellant argues that PRO539 is overexpressed along with 700 other molecules. Appellant argues that this provides utility for the nucleic acid, without any evidence that of the function or use (or even evidence of existence) of the protein encoded by PRO539. No evidence whatsoever was presented that regarding the function of the claimed PRO539 protein molecule, only speculation on the activity based upon the mRNA of PRO539.

The Federal Circuit then cited the Kirk decision,

**"We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates."**

376 F.2d at 942 (emphasis added).

Further, the Federal Circuit commented that Fisher failed to provide any evidence - test data, declaration, deposition testimony or otherwise - to support the uses argued as presently beneficial and practical. This same fact pattern applies to the current case. There is no test data, declaration, deposition testimony or any other evidence which supports any particular specific and substantial use for the protein of PRO539. The only test data is represented by a single point in which the mRNA of PRO539 is stated to be overexpressed in a single lung tumor from a single patient without any statistical significance.

When comparing the current case to Fisher, Nelson, Cross and Fujikawa, certain trends can be discerned. In each of the cases cited where utility was found, in vitro (and more often in vivo) testing of the specific molecule of interest demonstrated that the specific molecule functioned in a specific assay. As the Federal Circuit noted with regard to these cases when discussing them in Fisher, "In Jolles, Nelson, and Cross, the applicants disclosed specific pharmaceutical uses in humans for the claimed compounds and supported those uses with specific animal test data, in vitro, in vivo, or both." Fisher at 1234.

This is similar to the cited Cross v. lizuka case where specific inhibition of thromboxane synthetase was demonstrated for utility of the compounds. This is worlds apart from the current situation where no result whatsoever is shown for the claimed protein of PRO539. No therapeutic or functional utility is even alleged other than the concept that the PRO539 protein or antibody may be diagnostic of cancer, for which no evidence of any utility has been provided. The closest asserted utility is for the PRO539

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nucleic acid, and this utility, for the reasons extensively discussed in the rejection, above and previously, does not carry over into the protein.

The conclusion that is reached is that it is NOT more likely than not that there is a "reasonable probability" that the asserted utility for the proteins is true. No evidence whatsoever has been presented about the claimed protein of PRO539. All of the evidence is directed towards other molecules which themselves may or may not have utility, but which do not provide specific utility for the PRO539 protein.

#### **Weight of prior art**

Applicant submits that the Examiner has overlooked the ample information provided in Example 30 for determining whether a gene is significantly overexpressed. In particular, the specification at page 135 offers ample information on how to ascertain the "cutoff ratio" for hybridization. Appellant further submits the specification provides very clear guidelines as to how high levels must be to be deemed "significant".

Applicant's argument has been fully considered, but is not deemed to be persuasive because the specification discloses that if the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of probe from control (normal tissue) sample, the gene or genes overexpressed in the disease are identified (lines 22-24 of page 134). The specification fails to disclose the specific "cutoff ratio". Is the "cutoff ratio" 1-fold, 5-fold, 10-fold, or 100-fold difference? The art cautions researchers from drawing conclusions based upon small changes in transcription levels between normal and cancerous tissue. For example, Li, Ding and Sawiris demonstrate

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that simple overexpression alone is insufficient to demonstrate association with disease. As noted above, only 143 out of 2000 genes in the comparison by Li of colon cancer with normal were identified as being useful in the diagnostic analysis of colon cancer. If the "cutoff ratio" were disclosed in the specification to be statistically significant in a statistically significant sample population, the fact pattern would be different. In the current case, there is no evidence that the overexpression has any diagnostic significance and there is ample evidence in the art of Li, Ding and Sawiris that overexpression alone, without further analysis, lacks diagnostic significance.

When Applicant argues at page 12, for example, that there is a significant difference in PRO539 gene expression between the various tumor samples and the universal normal control, this statement lacks any basis in the specification or in any other evidentiary showing. First, the use of the plural "tumor samples" lacks evidentiary support. A better statement would be the "single prostate tumor sample from the single patient". There is no evidence of any statistical measurement. A cutoff ratio is not a statistical measurement of significance. It is simply an arbitrary selection, as shown by Li, where in 2000 genes known to be overexpressed in cancers, only 143 were diagnostic for colon cancer. Li showed that only 28 of more than 8000 genes (non-selected) were diagnostic for breast cancer. The evidence does not support Appellant's position on significance. Li, Ding and Sawiris each individually, and collectively demonstrate that simple cutoff type measures do not provide diagnostically significant data. These three references, written by experts in the microarray art, rebut example 30's simple "cutoff ratio" as a test for diagnostic significance.

Applicant argues the Meric, Gokman-Polar, Pennica and Konopka references, by trying to argue, for example, that "Pennica et al has no teaching whatsoever about the correlation of mRNA expression and protein expression in general. (see page 13 of response). There is no doubt that each of these references are drawn to specific protein molecules. The references simply represent individual demonstrations of situations where proteins and mRNA are not correlated in abundance. Applicant attempts to rebut with other references which show the contrary fact pattern.

Applicant cites to 149 references, most of which are submitted as abstracts, in order to support the position that there is a concordance between mRNA expression and protein expression. Applicant specifically addresses only a fraction of these references. None of these references, other than Orntoft, represents the sort of global comparison of many (as many as 2501) different proteins to their corresponding mRNAs that was performed by the microarray comparison papers cited in the action above. Applicant selectively chooses art to support one position, rather than attempting to balance all of the art and determine the consensus of opinion. In the utility analysis, all of the microarray papers, including the Polakis data, were analyzed in a combined fashion, where the raw data was available, in order to provide as objective an opinion as possible. Attempts to overload the examiner with prior art, particularly where all of the prior art does not even support the position taken (as will be discussed below), are not persuasive.

The citation to the textbooks is inappropos, because the textbooks trail the prior art. For example, even in the fourth edition of Cell, the text fails to teach newly

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discovered methods of posttranscriptional control such as SiRNA. Currently, most of Art Unit 1635 is devoted to the analysis of patent applications drawn to various forms of SiRNA, which is a very significant posttranscriptional regulatory process that could result in differential mRNA and protein levels. This entirely new technology is not appreciated by the textbook. Further, the texts fail to provide any specific relationship or showing supporting the position of Applicant that it is "more likely than not" that mRNA levels are associated directly with protein levels and that this functions properly as a proxy which can then itself be used for diagnosis.

#### **Microarray References**

Applicant then attacks a variety of the microarray references of Czupalla, Chen, Ginestier, Washburn, Anderson, Conrad and Kwong. All of Applicant's arguments are essentially spurious. Applicant does not rebut the basic factual point that each of these references support, which is that when large numbers of proteins are analyzed for expression alongside large numbers of nucleic acids, there is no correlation in expression. This result is repeated in essentially every large scale study cited and is true in additional uncited studies. The data is clear. To reiterate just one of the papers, Chen notes "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein. (see page 311, column 1)" Chen continues a little later "The majority of protein isoforms, however, did not correlate with mRNA levels and thus their expression is regulated by other mechanisms.

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We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression values (see page 311, column 1)."

This data is significantly superior to any presented by Applicant in rebuttal.

**Support by Prior art**

Many of the papers cited by Applicant fail to support the proposition made by Applicant. For example, Gromova et al was cited by Applicant, but Gromova et al believes that mRNA data alone is insufficient for prognostic value of molecules in cancer diagnosis noting "Considering the potential prognostic value of A-FABP protein and /or mRNA in TCC progression, it was important to determine if the levels of both types of macromolecules correlated both in the non-invasive and the invasive lesions expressing and lacking A-FABP. The need for such correlation was underlined by recent studies of Anderson and Seilhamer, who reported a lack of overall correlation between the mRNA and protein levels of 45 rat proteins analysed by 2D PAGE in combination with cDNA arrays (see page 83, column 2)."

Aust et al notes "Furthermore, the discrepancy between elevated TIMP-1 mRNA levels of thyrocytes and the extremely low TIMP-1 protein secretion by these cells is difficult to explain. Post transcriptional regulatory events may be responsible for this confounding result (see page 722, column 2).

Kuo et al stated "Comparison of the gene and protein expression profiles showed that there was a discordance between mRNA and protein levels (see page 904, column 1).

Therefore, the rejections are maintained.

***Conclusion***

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.


7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.



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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jeffrey Fredman  
Primary Examiner  
Art Unit 1637

12/2/05